directed to specific γ-conopeptides having no variable amino acid residues are enabled by the specification and would be allowed, the specification does not reasonably enable claims directed to specific γ-conopeptides having variable amino acid residues as recited in claims 20-26. Thus, according to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

In rejecting claims 20-26, the Examiner referred to the reasons for rejection previously provided in Paper No. 20, and responded to Applicants' arguments set forth in Applicants' response filed October 24, 2001. The Examiner characterized the Applicants' previous remarks as arguing that the claimed substitutions are well known in the art of conopeptides and that the Shen, et al. reference does not teach that slight species variation in the hypervariable loop regions can result in distinct pharmacological activities. In the May 21, 2002 Final Office Action, the Examiner expressed disagreement with this argument. The Examiner further stated that the fact that the substitutions are well known is not relevant because the substitutions were made in other distinct conopeptides that only share common source of material, not biological activity, as taught by Shen, et al.

In response, Applicants respectfully traverse the rejection of claims 20-26 under 35 U.S.C. § 112, first paragraph. Applicants maintain that the claims as written are fully enabled by the specification. In traversing the rejection, Applicants reiterate the remarks set forth in the October 24, 2001 response and provide the additional following comments.

The section in the Shen, et al. review to which the Examiner refers discusses slight species variations arising from hypermutation and natural selection to allow slight changes in pharmacological activities (stated as "distinct pharmacological activities" in the paper). Shen, et al. goes on to state, "As new pharmacological targets have evolved in prey species, the high rate of mutation in the mature peptide has enabled the snails to optimize venom components for new receptor subtypes." It is clear that the intent of this section was to discuss fine-tuning of conotoxin activity against closely related subtypes of a class of receptor and not to say that the slight variations

result in "distinct" pharmacological activities per se. Applicants believe that the Examiner has taken this discussion out of the context in which it was presented. The Examiner attempts to claim that the variations within a conotoxin family give rise to pharmacological diversity (e.g., having very different targets), when, in fact, the point of the Shen, et al. paper is that a given family of conotoxins will all target the same type of receptor. The variations in sequence allow the snail to closely track evolutionary changes between prey types. For example, ALL 3/5 α-conotoxins target the neuromuscular nicotinic acetylcholine receptor to give rise to flaccid paralysis of prey. However, each 3/5 α-conotoxin may be more or less active on neuromuscular nicotinic acetylcholine receptors from a variety of species. For example, some 3/5 α-conotoxins inhibit fish muscle while being much less potent (but still effective) at inhibiting muscle in mammals, while other 3/5 α-conotoxins are equally effective or more effective at inhibiting mammalian neuromuscular nicotinic acetylcholine receptors than they are at inhibiting fish receptors. This variation in selectivity does not at all mean that one α-conotoxin acts on a different receptor than another or that one α-conotoxin would not be able to block mammalian nicotinic acetylcholine receptors just because it was not as effective as another. It simply means that there are some subtle differences in the potency and selectivity of each 3/5 α-conotoxin, but they ALL inhibit neuromuscular nicotinic acetylcholine receptors. Furthermore, it is known that substitution of Hyp for Pro, Gla for Glu, Bromo-Trp for Trp in a conotoxin (regardless of family) results in only slight changes in pharmacologic activity (i.e. the peptide may have slightly higher or lower activity for its receptor. However, in no case to date of which Applicants are aware, have these conservative mutations been shown to abolish or dramatically change the activity of a conotoxin peptide. Thus, a γ-conotoxin would still be expected to target the pacemaker channels regardless of the substitution made and one skilled in the art would predict (and would be correct in his assumption) that the γ-conotoxins with the slight variations would still have activity on pacemaker channels. Accordingly, claims 20-26 are fully enabled and thus satisfy the requirements of 35 U.S.C. § 112, first paragraph. Applicants therefore respectfully request that the Examiner reconsider and withdraw the claim rejections.

In view of the above remarks, it is believed that the claims satisfy the requirements of the patent statutes and fully address the Examiner's concerns as set forth in the Final Office Action of May 21, 2002. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

RESPECTFULLY SUBMITTED,			
NAME AND REG. NUMBER	Patrick T. Skacel, Reg. No. 47,948		
SIGNATURE		*DATE*	November 21, 2002

Address	ROTHWELL, FIGG, ERNST & MANBECK, pc 1425 K Street, N.W., Suite 800				
City	Washington	*State*	D.C.	*Zip Code*	20005
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031

147A.am3